Mechanism of Respiration

(A) Inspiration:

1- Normal quiet breathing (= eupnea):

It is an active process initiated by:

a- +++phrenic nerve (C_{3-4-5}) → the dome of diaphragm moves downward → +++ the vertical diameter of the thorax (75% of intrathoracic volume change).

b- +++spinal nerves → external intercostal muscles move the ribs upward & outward → +++ the antero-posterior & transverse diameters of the thorax.

2- Forced inspiration:

Strong contraction of diaphragm; external intercostals; sternomastoid (lift sternum upward), anterior serrati (lift ribs upward) & scalene (lift 1^{st} & 2^{nd} ribs upward)

(B) Expiration:

1- Normal quiet breathing:

Expiration is passive. Relaxation of inspiratory muscles → lungs recoil → push air out

2- Forced expiration

Contraction of internal intercostals (pull rib cage downward) & abdominal muscles (+++ intra-abdominal pressure) → push the diaphragm up → ---- thoracic volume

- Expiratory muscles work during exercise & voluntary forced expiration;
- Expiratory muscles **work at rest**→ in bronchial asthma; in emphysema; pulmonary fibrosis & congestion.

Pulmonary pressures

Intra-Alveolar Pressure (P_{alv}): pressure of air in the alveoli

Changes in Intra-Alveolar Pressure: caused by changes in lungs volume

Boyle's law: for a given quantity of any gas (such as air) in a container, the pressure is inversely related to the volume of the container.

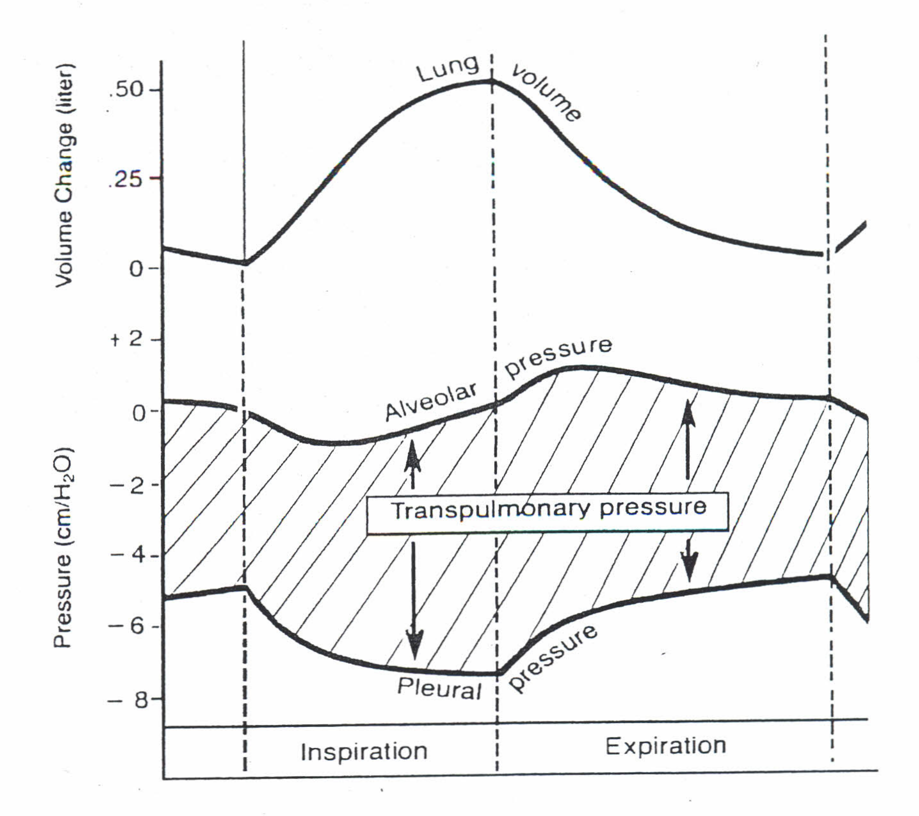
a- During inspiration, $P_{alv} = -1 cmH_2O$ ($P_{atm} > P_{alv}$) → inspiration occurs.

b- During expiration, $P_{alv} = +1 cmH_2O$ ($P_{alv} > P_{atm}$) → expiration occurs.

c- At end of inspiration & expiration (between breaths) $P_{alv} = P_{atm} = 0$ pressure

The Intra Pleural Pressure (IPP): pressure inside the pleural space

- It is always negative under normal conditions.
- At end of normal expiration → - 3 cmH_2O.



Volume Change (liter)
.50
.25
0
Lung
volume
Pressure (cm/H2O)
+ 2
0
− 2
− 4
− 6
− 8
Alveolar
pressure
Transpulmonary pressure
Pleural
pressure
Inspiration
Expiration

- At the end of normal inspiration → -6 to -8 cmH_2O.
- Muller's experiment (forced inspiration with closed glottis)→ -30/-40 cmH_2O
- Valsalva's experiment (forced expiration with closed glottis) → +50cmH_2O
- Emphysema → --- recoil tendency of lungs → IPP becomes less negative.

Functions of intra-pleural pressure:

(1) It helps lung expansion.

(2) It helps venous and lymphatic return to the heart.

Causes of negativity of intra-pleural pressure:

- Continuous tendency of lungs to recoil inward against continuous tendency of chest wall to expand outward.

Causes of recoil tendency of lungs & expansion tendency of thoracic wall:

(1) Elastic tissues in & chest wall:

- Both lungs & thoracic wall are elastic & have a relaxation volume where they are neither stretched nor compressed.
- Relaxation volume of lungs → 1 liter, while that of thoracic wall → 5 liters.
- At end of expiration → volume of lungs & thoracic wall = 2.3 liters.
- Lungs are partially stretched and tend to recoil inward.
- Thoracic wall is partially compressed & tends to expand outward.

(2) The surface tension of the fluid lining the alveoli:

- Alveolar cells are lined with water (moist).
- At air-water interface → +++ surface tension → strong inward force → collapse
- Type II alveolar cells → surfactant → ---- surface tension → facilitates lung expansion during inspiration

Pneumothorax: Presence of air in the intra-pleural space.

a) External or opened pneumothorax:

If pleural sac is broken (knife) → IPP will equilibrate with P_{atm} (air fills pleural sac)

b) Internal or closed pneumothorax:

If a disease (pneumonia) damages the wall of pleura near a bronchus or alveolus → air from inside the lungs enters the intrapleural space

Effects of pneumothorax:

1- The lungs collapse; while the chest wall expands

2- ------venous return & lymph flow.

(4) Transpulmonary (Transmural) Pressure (P_{TM}) (P_{alv} - $P_{I.p}$):

- Pressure difference in between the intra-alveolar and the intra-pleural pressure
- P_{TM} at end of normal expiration= $P_{alv.} - P_{I.p.}$= 0 cmH_2O- (-3 cmH_2O) = 3 cmH_2O
- P_{TM} at end of normal inspiration= $P_{alv.} - P_{I.p.}$= 0 cmH_2O- (-8 cmH_2O) = 8 cmH_2O
- It is the force acting to expand the lungs
- It is opposed by elastic recoil of partially expanded (partially stretched) lungs.

Surfactant

Nature of surfactant:

- Formed of phospholipid: **dipalmitoyl-phosphatidylcholine (DPPC).**
- Hydrophilic part → towards the fluid lining the alveoli & the hydrophobic part → towards the air in the alveoli.
- Phospholipid molecules → form a layer between air & fluid lining the alveoli → ----- surface tension

Functions of surfactant:

(1) Facilitation of lung expansion:

---- surface tension → facilitates & ---- the effort for lung expansion during inspiration

(2) Prevention of alveolar collapse during expiration.

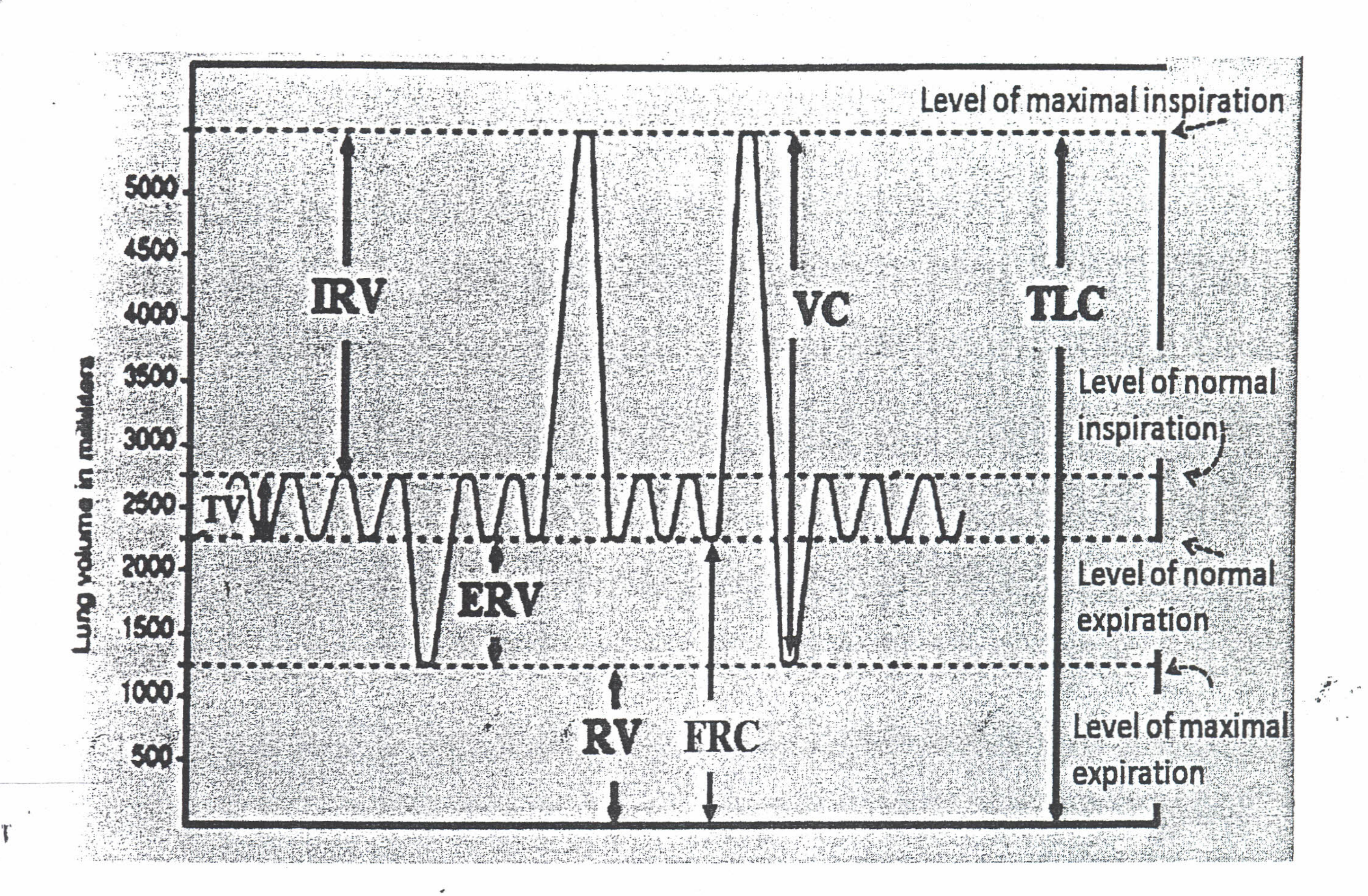
During expiration → surfactant molecules move closer together → ---- surface tension → prevents alveolar collapse.

(3) Prevention of pulmonary edema:

Surfactant → ---- surface tension → ---- filtering force → prevent pulmonary edema

Surfactant deficiency occurs in the following conditions:

1. **Respiratory distress syndrome (RDS): (hyaline membrane disease) in premature infants** (2nd leading cause of death): In fetus, surfactant is secreted at week 24 & is mature at week 35
   - Mature surfactant → Lecithin : sphyngomyelin ratio > 2:1 in amniotic fluid


Level of maximal inspiration
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
Lung volume in milliliters
IRV
VC
TLC
TV
ERV
RV
FRC
Level of normal inspiration
Level of normal expiration
Level of maximal expiration

- ---- surfactant → lung collapse (atelectasis) & hypoxemia.

2. Long-term inhalation of 100% oxygen & pump oxygenator in cardiac surgery.
3. Occlusion of 1 branch of pulmonary artery (thrombus)
4. Cigarette smoking.
5. Hypothyroidism: thyroxine is important for surfactant production
6. Hypocorticism: cortisol accelerates maturation of surfactant.
7. Hyperinsulinism: insulin inhibits surfactant secretion (+++RDS in infants born to diabetic mothers (fetal hyperinsulinism)).

Pulmonary volumes & capacities:

Measured using a spirometer: volumes would be 10% smaller for a female.

A] Pulmonary volumes:

1. **Tidal volume TV:** volume of air inspired or expired at rest = 500 ml.
2. **Inspiratory reserve volume IRV:** maximum volume of air inspired forcibly after normal inspiration = 3000 ml.
3. **Expiratory reserve volume ERV:** maximum volume of air expired forcibly after normal expiration = 1100 ml (---- in asthma & emphysema)
4. **Residual volume RV:** Volume of air remaining in lungs after maximum expiration = 1200 ml. (20% of total lung capacity)
   - **Importance**: aerates blood between breaths
   - **Increased in**: asthma and emphysema (up to 70% of total lung capacity)
   - **Can't be measured** by spirometry
   - **Calculated** by helium dilution method.
   - **Minimal air:** Small volume of air remaining in lungs even after opening of chest wall & lung collapse

     Medicolegal importance: if lung floats in water it indicates that infant was born alive & has taken breath. If lung sinks in water, infant was born dead.

B] Pulmonary capacities: sums of more than one lung volume

1. **Inspiratory capacity (IC):** maximum volume of air inspired at end of normal expiration: IC = TV + IRV = 3500 ml.
2. **Vital capacity (VC):** maximum volume of air expired following a maximum inspiration: VC = VT + IRV + ERV = 4600 ml.

3. **Functional residual capacity (FRC)**: volume of air remaining in lungs at end of normal expiration (between breaths; relaxed respiratory muscles): FRC = ERV + RV = 2300 ml. It can't be measured by spirometry

4. **Total lung capacity (TLC)**: volume of air in lungs at end of maximum inspiration: TLC= TV+IRV+ERV+RV= 5800ml. It can't be measured by spirometry

Factors affecting the vital capacity:

Clinical significance of VC: Index about the strength of respiratory muscles

Physiologic variations of VC		Pathologic variations of VC
increases in	**decreases in**	a- Paralysis or myositis of respiratory muscles
a- Males. b- Athletes. c- Standing position (free descent of diaphragm)	a- Females. b- Recumbent position, pregnancy.	b- Bone deformities (kyphosis, scoliosis) c- Loss of lung elasticity e.g. emphysema. d- Restrictive lung diseases e.g. lung fibrosis. e- Obstructive lung diseases, e.g., asthma. f- Abdominal tumors

Timed vital capacity:

- Maximum inspiration → then exhales as hard & as completely as possible
- Volume exhaled in 1st sec → forced expiratory volume in 1 second (FEV_1)
- Total volume exhaled → forced vital capacity (FVC)
- FEV_1 is about 80% of the FVC.
- Restrictive lung diseases (fibrosis) → ---- FEV_1 & FVC but normal or +++ FEV_1 / FVC %
- Obstructive lung diseases (asthma) → ---- FEV_1 & FVC but low FEV_1 / FVC %

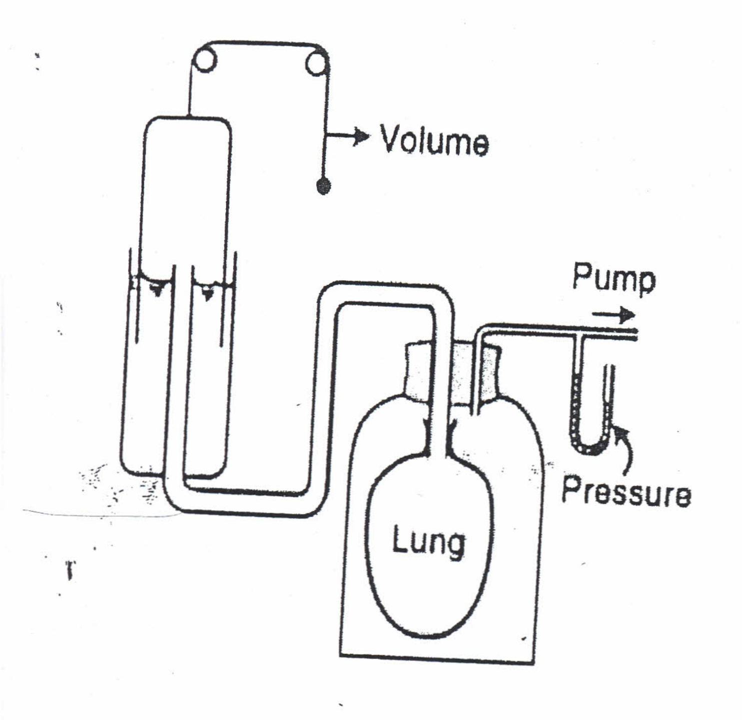
Minute Ventilation: minute respiratory volume

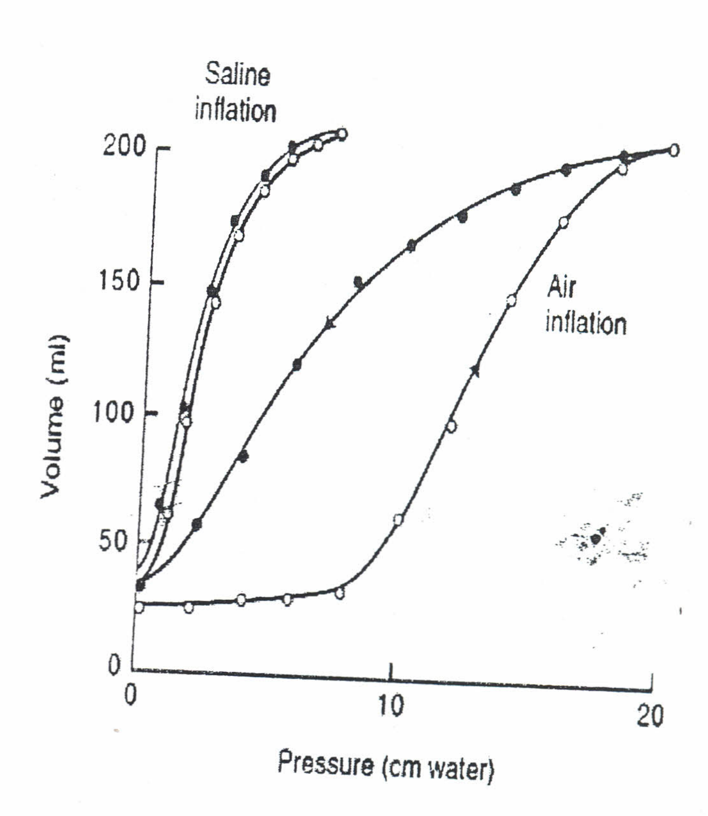
- Total volume of air that flows into & out of the respiratory system in 1 minute
- Minute ventilation = TV x Respiratory rate = 500 x 12 = 6000 ml / min.

Compliance (C)

Lung Compliance

- Distensibility (stretchability) of the lungs => change in lung volume (ΔV_L) in response to unit change in transmural pressure => $C = \Delta V_L / \Delta P_{TM}$
- Compliance is the slope of the pressure volume curve.
- Compliance is the reciprocal of **elastance** (= elastic resistance to expansion)


Volume
Pump
Pressure
Lung


Saline
inflation
Air
inflation
Volume (ml)
Pressure (cm water)
200
150
100
50
0
0
10
20

- Elastance depends on amount of elastic tissue. The greater the elastic tissue => the greater its tendency to recoil => the lower its compliance

Normal values of compliance:

- Normal lung compliance => 200 ml/cmH_2O.
- Normal chest wall compliance => 200 ml/cmH_2O.
- Normal compliance of lungs + chest wall => 100 ml/cmH_2O.

➢ Static lung compliance:

A-Pressure-volume relationship in excised lung (animal):

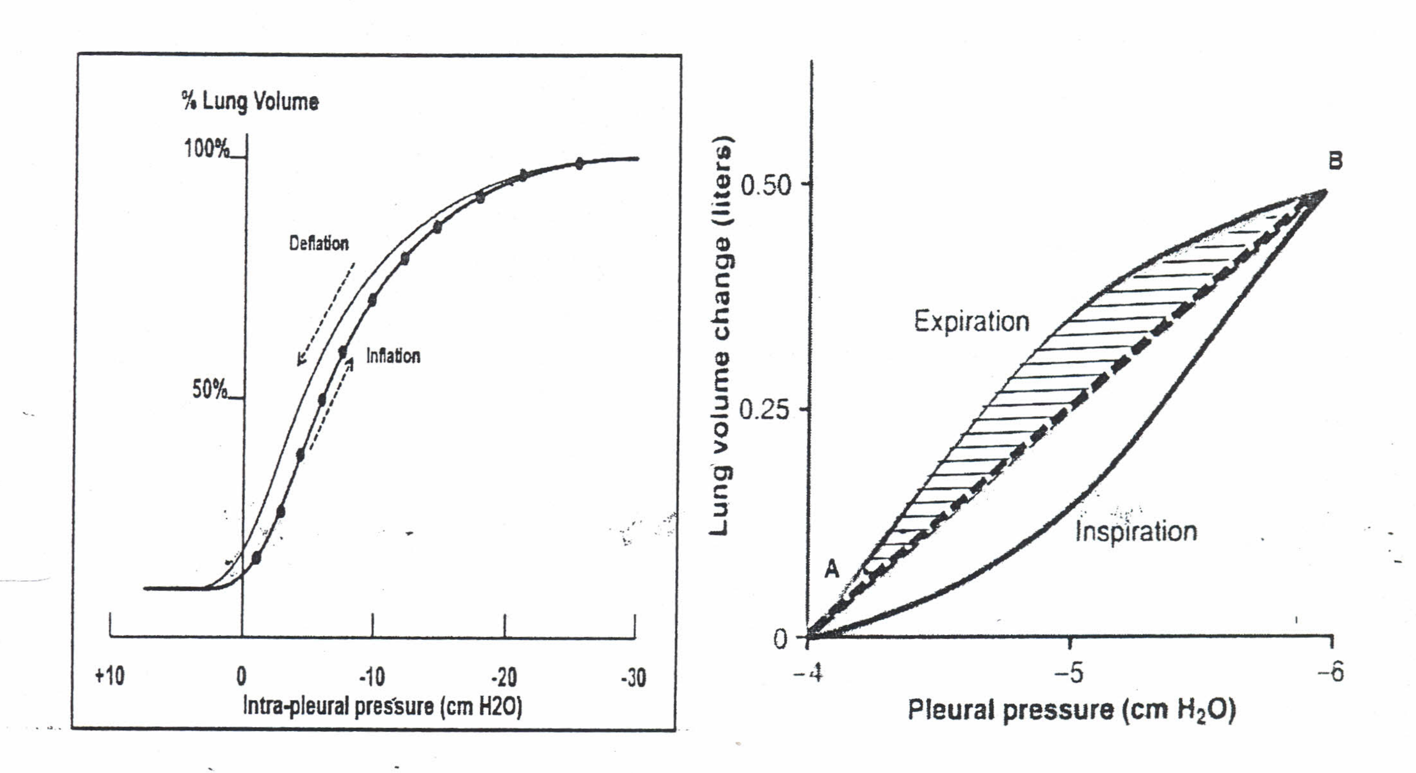
1. Change the pressure outside the lung by a vacuum pump (like changes in IPP)
2. Negative pressure outside the lungs => lungs expands & +++ lung volume
3. Positive pressure outside the lung => lungs collapses & --- lung volume
4. Changes in lung volume => measured with a spirometer.
5. After pressure change → wait enough time before record of volume change because it takes time to occur due to resistance to air flow in & out.
6. **2 observations can be made on the recorded curve:**
   a. Pressure-volume curve is S-shaped (not linear), especially the inflation curve
      - Low expanding pressure => low slope => difficult to open small alveoli.
      - Middle range of pressure => greatest slope => lungs are most distensible
      - High expanding pressure => flat curve => maximum air filled alveoli => stiff

   b. **Hysteresis** → inflation & deflation curves are different due to:

      More ----- in surface tension during deflation (surfactant molecules become closer) => at same pressure, lung contains more air volume during deflation
7. Inflation by saline (no surface tension) => less observed hysteresis → inflation occurs by less pressure
8. Surface tension => major force resisting lung inflation & main cause of hysteresis

B- Static Lung Compliance in living subject:

- Lung is inflated or deflated by changing transmural pressure in small steps,
- Measurements of volume after each step following stabilization of lung volume
- Depends on elastic resistance of the lung (tissue elasticity + surface tension)
- Pressure volume curve shows hysteresis (as above)
- Compliance is taken as the slope of deflation curve.



Dynamic pressure-volume curve of the lung during a single normal tidal breath. *The dashed line (AB) is the compliance line.*

➢ Dynamic lung compliance:

- Pressure-volume relationship is measured during continuous non-interrupted inflation & deflation (during actual air flow)
- Hysteresis loop is more observed during inspiration & expiration
- Inspiration & Expiration curves => bent below & above the straight line of static compliance because more change in IPP is needed to overcome the **frictional resistance** & **lung viscosity** resistance to air flow
- Inspiration & expiration curves coincide with the straight line at end of air flow

Factors affecting lung compliance:

Static lung compliance		Dynamic Lung compliance
decreases in	**increases in**	**decreases in**
• Restrictive lung disease (pulmonary congestion, fibrosis) • Deficiency of surfactant (RDS) +++ surface tension force	Emphysema & old ages => --- lung elasticity => ---tendency to recoil => **higher FRC** => **barrel-shaped** chest (higher air volume)	- Increased airways resistance e.g. bronchial asthma. - Rapid breathing (more frictional resistance) Emphysema. Loss of elastic tissue => +++ resistance to airflow especially during expiration

Factors affecting compliance of thoracic wall	
decreases in	**increases in**
• Skeletal muscle diseases (myositis, poliomyelitis) • Arthritis, kyphoscoliosis • Obesity.	Athletes

Work Of Breathing

I- During inspiration:

(1) **Compliance / elastic work:** 65% of the work to expand the lungs

(2) **Airway & Tissue resistance work**: 35% of total work

II- During expiration:

- During quite expiration → the energy stored in expanded elastic structures is released during expiration => no muscular work is performed => passive

- Bronchial asthma or rapid deep breathing in exercise => +++ the work to overcome frictional resistance during inspiration & expiration

The work of breathing is increased when:

1. The compliance is reduced, e.g., surfactant deficiency and lung fibrosis
2. The air passages are narrowed, e.g., in bronchial asthma.

Airway resistance:

- The greatest resistance is met in medium-sized bronchi.
- Low resistance inside small bronchioles (large number & cross sectional area)

Factors affecting the diameter of airway passages:

Bronchodilatation	Bronchoconstriction
a) +++ Sympathetic → noradrenaline → ++ β_2 adrenergic receptors. b) Lung expansion → traction on walls of airways increasing their diameter.	a) +++ Vagus → acetylcholine → ++ cholinergic receptors. b) ---- PCO_2 in alveolar air c) Allergy → histamine release

Dead Space

Part of respiratory system where no gas exchange takes place (wasted ventilation)

Types of Dead Space:

1- Anatomic Dead Space:

- Air filing up the airways in the conducting zone = 150 ml (30% of TV 500ml)

2- Alveolar Dead Space:

- Air in non-functioning alveoli which have little or no blood supply.
- Physiologic dead space = anatomic dead space + alveolar dead space.
- Normally: physiologic dead space = anatomic dead space.
- Lung diseases: physiologic dead space > anatomic dead space

Significance = Importance of dead space:

A. Difference in composition between inspired, alveolar & expired air:

During inspiration:

- Conducting zone at end of expiration is full of hold air (less O_2 & more CO_2 than atmospheric air).
- Next inspiration, 350 ml fresh air mix with 150 ml of old air & move into alveoli

- PO_2 in inspired air > in alveolar air while PCO_2 in inspired air < in alveolar air.
- Alveolar ventilation = (Tidal vol. - Dead Space) x Respiratory rate
  = (500 ml - 150 ml) x RR = 350 ml x 12 breaths/min = 4200 ml/min

During expiration,

- 350 ml of alveolar air mix with 150 ml air in dead space (contains atmospheric air from previous inspiration: high O_2 & low CO_2) → expired
- PO_2 in expired air > in alveolar air while PCO_2 in expired air < in alveolar air.

B. Differences in alveolar ventilation in various breathing patterns:

- Shallow rapid breathing => ---- alveolar ventilation => hypoxia & hypercapnia;
- Slow deep breathing => +++ alveolar ventilation.
- +++ depth of breathing (+++ TV) is more effective in +++ alveolar ventilation than +++RR (athletes)

C. Protective function:

1. Humidification and warming of inspired air.

2. Warming of inspired air.

3. Removal of foreign particles from air:

a- Particles > 10 μ in size => filtered by hair in nose & stick to nasal mucus

b- Particles: 2 to 6 μ:

-In upper airways → stick to mucus → expelled by coughing or sneezing

-In conducting zone → mucus escalator → pharynx → swallowed or expectorated

c. Particles: 2 to 0.5 μ => phagocytosed by dust cells in alveoli.

d. Very small particles < 0.5 μ => suspended in air & exhaled during expiration.

Exchange of Gases in the Lungs

Diffusion of gases through respiratory (pulmonary) membrane:

Respiratory membrane is formed of the following layers:

1. A layer of fluid containing surfactant lining the alveolus.
2. Alveolar epithelium formed of one layer of epithelial cells.
3. Epithelial basement membrane.
4. Thin interstitial space between alveolar epithelium & capillary membrane.
5. Capillary basement membrane.
6. Capillary endothelial cells.

- Thickness of respiratory membrane is about 0.2 μm

- Surface area of respiratory membrane is 100 m^2 (300 million alveoli).

Blood traverses 1 pulmonary capillary in 0.75 second:

- Under resting conditions, complete equilibration between alveolar & capillary PO_2 occurs after 0.25 second (1/3 cardiac cycle)
- Equilibration of CO_2 occurs at the same rate as O_2 in spite of the higher solubility of CO_2 and its greater rate of diffusion than O_2.

This is primarily due to:

- Pressure gradient for CO_2 (6 mmHg) while that for O_2 (60 mmHg).
- CO_2 transported in blood as bicarbonate → takes time to be reversed to CO_2
- CO_2 molecular size is 1.4 times greater than O_2)
- CO_2 is more soluble in water than O_2 and diffuses 20 times faster than O_2

Factors affecting rate of gas diffusion through respiratory membrane

A- Rate of diffusion is directly proportional to:

1- Diving pressure across the alveolar-capillary membrane = difference in partial pressure of gas between alveoli (P_A) and capillary blood (P_C)

- Net O_2 diffusion occurs from alveoli into blood (P_A (105mmHg) > P_C (40mmHg))
- Net CO_2 diffusion occurs from blood into alveoli (P_C (46mmHg) > P_A (40mmHg))

2- The surface area of the respiratory membrane:

- Diffusion decreases in emphysema & lung collapse (---- surface area)
- +++ Surface area during exercise:
  - opening of the closed pulmonary capillaries
  - dilatation of the already opened capillaries.

3- Temperature.

4- Solubility of the gas in the medium

B- Rate of diffusion is inversely proportional to:

1- Square root of **molecular weight**.

2- **Thickness** of membrane (0.2μ): it increases with edema and lung fibrosis.

$$RD \ \alpha \ \frac{(P_1-P_2)\,T.A.S.}{\sqrt{m}L}$$

Where:

$P_1 - P_2$ = Pressure difference (ΔP)

T = Temperature

A = Surface area of the membrane

S = Solubility of the gas in the medium

$\sqrt{m}$ = Square root of molecular weight

L = Length (thickness of membrane)

Alveolar Ventilation (V_A) Perfusion (Q) Ratio (V_A/ Q)

- Normally alveolar ventilation is 4L/min & pulmonary perfusion is 5L/min.
- Ventilation /perfusion ratio in the lung as a whole is 0.8.
- Ventilation and perfusion are not equal all through the lungs.
- They decrease from base toward apex in the upright lung, but the rate of decrease of blood flow exceeds the rate of decrease of ventilation.
- In lung apex, blood flow is relatively poor compared to ventilation (high $V_A/Q = 3$)
- At lung base, blood flow is relatively high compared to ventilation (low $V_A/Q = 0.6$)

Causes of regional differences in lung ventilation:

- Under effect of its weight, the lung tends to droop => widen the pleural space around the apex => more −ve pressure (-10 mmHg). While the pleural space around the base becomes narrower => less −ve pressure (-2.5 mmHg)
- Apical alveoli are, more expanded than basal alveoli at start of inspiration.
- With inspiration → Δ V at apex is less than Δ V at the base
- Thus, the ventilation at the base is highest and at the apex is lowest.

Causes of regional differences in blood perfusion:

- Blood pressure inside capillaries → distending pressure
- Alveolar pressure outside capillaries → compressing pressure
- At lung apex → --- pulmonary arterial pressure (due to gravity) & +++ alveolar pressure (distended alveoli) → capillaries nearly close.
- At lung base → +++ pulmonary blood pressure & ---- alveolar pressure (less distended alveoli) → capillaries open & distend → +++ blood flow

Variations in V_A/Q

1- At ideal ventilation and perfusion

- V_A/Q is matched = 0.8 - 1.2
- Venous blood has a PO_2 of 40mmHg and a PCO_2 of 46mmHg.
- Arterial PO_2 becomes 100 mmHg and PCO_2 40 mmHg.

2- At normal perfusion with no alveolar ventilation (bronchial obstruction: V_A= zero):

- $V_A/Q = 0 /Q = 0$; Thus → ---- V_A/Q with ----- ventilation (obstruction of bronchus)
- PO_2 in alveolar air and arterial blood is 40 mmHg & PCO_2 is 46 mmHg (similar to venous blood), as atmospheric air can't reach the alveoli.

3- At normal ventilation, but no capillary perfusion (pulmonary thrombi: Q=zero):

- $V_A/Q = V_A/0 = \infty$; Thus → +++ V_A/Q when ---- blood flow (thrombus)
- The alveolar PO_2 is 152 mmHg and PCO_2 is 0 mmHg (similar to inspired air), since no O_2 extracted or CO_2 added (wasted ventilation)

4- Difference between arterial PO_2 (100 mmHg) & alveolar PO_2 (105 mmHg) = venous admixture:

a- **Difference in V_A/Q at different zones of the lung:**

- More blood (57%) comes from alveoli with low V_A/Q (low PO_2) at lung base
- Only 10% comes from alveoli with high V_A/Q (high PO_2) at lung apex

b- **Physiologic shunt:**

- 2-5% of venous return passes directly into arterial blood: **Examples:**
  - i- Bronchial veins draining upper airways pass directly into pulmonary veins
  - ii- Coronary venous blood that passes directly into left ventricle

Autoregulation of V_A/Q : Compensatory Mechanisms Matching V_A/Q

1. In Alveolar Hypoxia:

--- alveolar PO_2 (poorly ventilated alveoli) → arteriolar VC → redistribution of blood to capillaries of well-ventilated alveoli

2. In Alveolar Hypocapnia:

--- alveolar PCO_2 (over ventilation or --- perfusion) → airways constriction of these alveoli → redistribution of air to alveoli with a better V_A/Q

Oxygen transport by the blood

O_2 is transported in the blood in 2 forms:

1- O_2 in physical solution

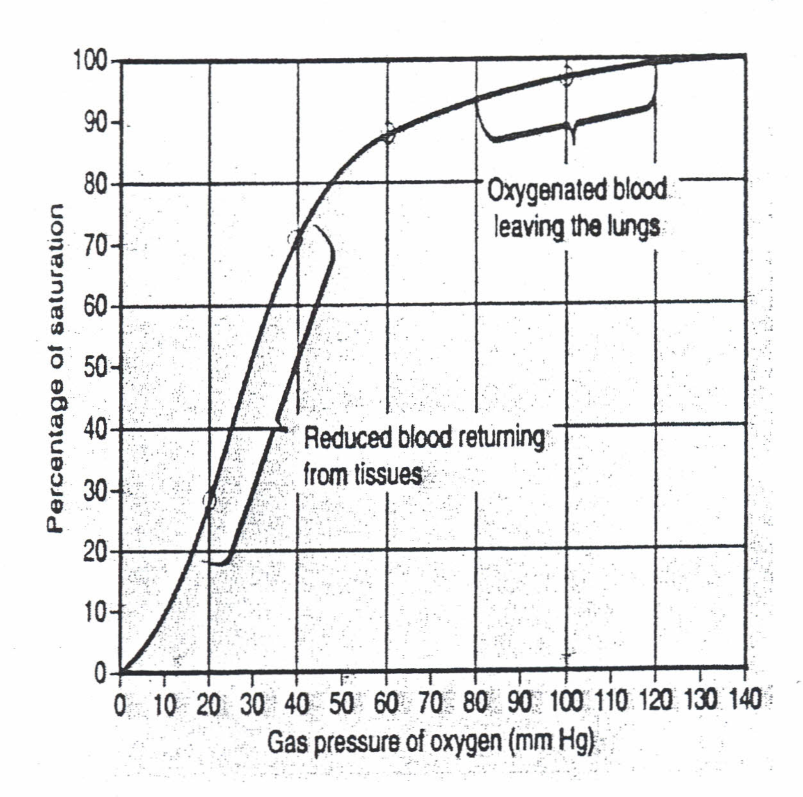
- 0.3 ml/100 ml arterial blood ; 0.13 ml/100 ml of venous blood.
- It determines blood PO_2 & diffusion direction of O_2.

2- **O_2 carried by hemoglobin:**

- 19.5 ml of O_2 /100 ml arterial blood (98%) → oxygenation not oxydation
- Hb → 4 Fe^{++} → can reversibly combine with 4 O_2 & remain in Fe^{++} state

O_2 content: volume of O_2 carried by Hb / 100 ml blood (ml O_2/100 ml blood)

O_2 capacity of blood: maximum volume of O_2 carried by Hb when fully saturated (varies with Hb content). 1gram Hb combines maximally with 1.34 ml of O_2.



100
90
80
70
60
50
40
30
20
10
0
Percentage of saturation
Oxygenated blood leaving the lungs
Reduced blood returning from tissues
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
Gas pressure of oxygen (mm Hg)

% saturation of Hb with O_2 (% HbO_2) doesn't vary with Hb content

$$= \frac{O_2 \text{ content}}{O_2 \text{ capacity}} \times 100$$

Hemoglobin O_2 dissociation curve:

- Relationship between PaO_2 and $\%HbO_2$ saturation is not linear but S shaped.
- % HbO_2 saturation is preferred to O_2 content as it doesn't change with change in Hb content (anemia)

Cause of the S shape of the O_2 dissociation:

- The 4 subunits of Hb load or unload their O_2 molecules with different affinities.
- +++ $PO_2 \rightarrow$ +++ saturation of same Hb molecule.

Physiologic Significance of S-shaped Hb-O_2 dissociation curve

- **At 100 mmHg PO_2**, Hb is approximately 97% saturated. Further increase in PO_2 => +++ O_2 in physical solution with little effect on the Hb-O_2 % saturation
- **At 60 mmHg PO_2**, Hb-O_2 % saturation = 90% => **flat portion (plateau)** of Hb-O_2 dissociation curve => alveolar & arterial PO_2 can decrease with little change in % HbO_2 saturation **(important in high altitude)**.
- **Below PO_2 60 mmHg**, desaturation of Hb is rapid **(steep portion)**
- **At 40 mmHg PO_2** => Hb-O_2 saturation = 70% **(in tissues during rest = venous blood)** => thus, tissues take about 27% of O_2 of arterial blood.
- **At 20 mmHg PO_2** Hb-O_2 saturation = 30% **(in tissues during exercise)**

Steep part of the curve → 60% of O_2 can be off-loaded with 40 mmHg change in PaO_2 (60 to 20 mmHg) => give more O_2 to metabolically active tissues with low PaO_2

Coefficient of O_2 utilization:

% ratio of volume of O_2 taken by tissues from arterial blood to total O_2 =

$$\frac{\text{Arterial } O_2 \text{ content - Venous } O_2 \text{ content (} O_2 \text{ utilized by tissues)}}{\text{Arterial } O_2 \text{ content}} \times 100 = 25\% \text{ at rest}$$

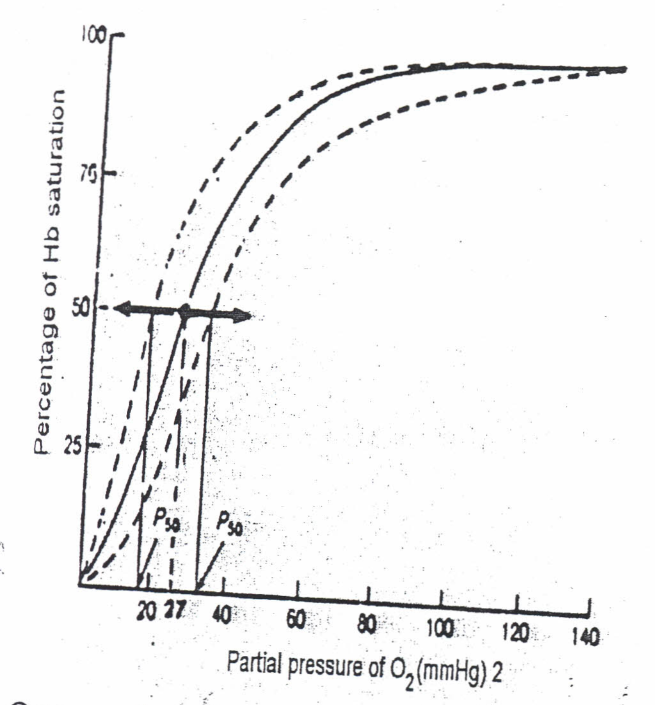
& up to 75% in muscular exercise. **It depends on:**

- Directly proportional to metabolic tissue activity.
- Inversely proportional to rate of blood flow.

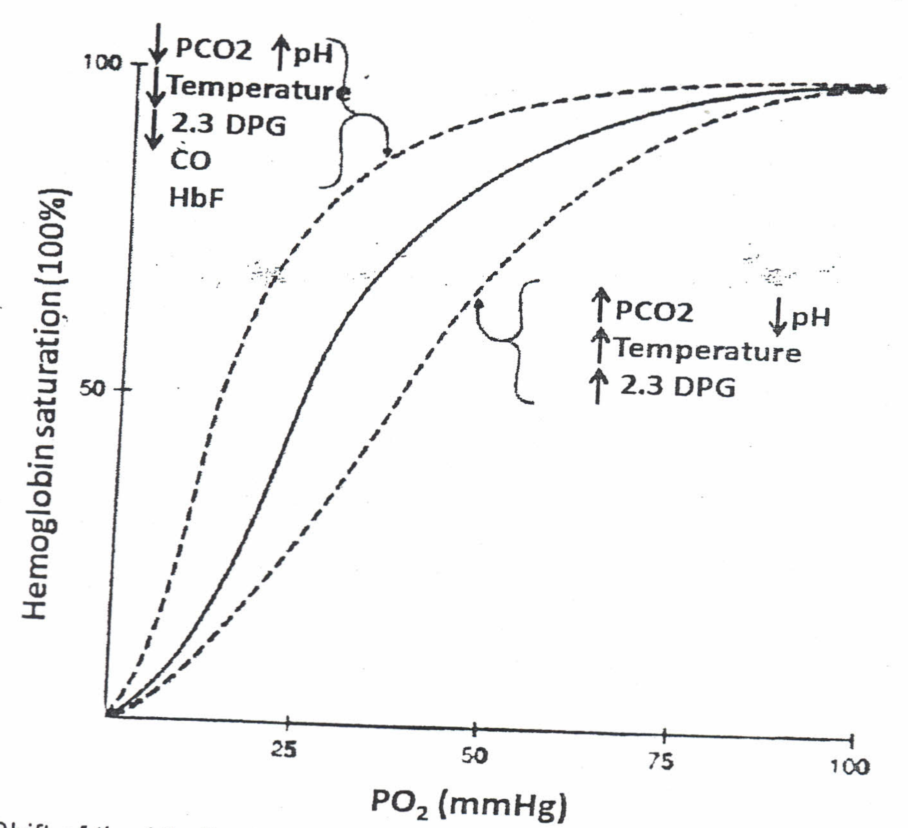
Shift of the Hemoglobin-O_2 Dissociation Curve

P_{50} = PO_2 at which Hb is 50% saturated

- P_{50} is an inverse function of the Hb affinity for O_2



Oxygen dissociation curve. PO_2 at which there is 50 percent saturation of hemoglobin with O_2 is called P_{50}. Right shift in the curve increases P_{50}, while left shift in the curve decreases P_{50}.



Shift of the Hb-O_2 dissociation curve to the right and to the left (dotted lines).

- The normal P_{50} for human blood is 27 mmHg.
- Hb with greater O_2 affinity → lower P_{50} (= shift to left).
- Hb with reduced O_2 affinity → higher P_{50} (= shift to right) =.

Factors that shift the curve to right Hb releases its O_2 at a higher PO_2	Factors that shift the curve to left Hb releases its O_2 at a higher PO_2
<u>1- +++ t° & PCO_2 & -----pH(+++H^+)</u> ▪ Effect of PCO_2 & pH → Bohr effect ▪ At a given PaO_2→ less O_2 bound to Hb ▪ Muscular exercise → +++ t°; PCO_2; --- pH → more O_2 released to active muscle. ▪ CO_2 & H^+ → change Hb shape → facilitate the off loading of O_2. <u>2- Effect of 2,3-DPG</u>: ▪ It is an end product of RBCs metabolism ▪ 2,3-DPG bind to β chains in deoxygenated form → --- the affinity of Hb to O_2. ▪ facilitates the off loading of O_2 from Hb ▪ hypoxia (at high altitudes) or exercise → +++ 2,3-DPG → shift to right.	<u>1- ----- t° & PCO_2 & +++ pH (----H^+)</u> ▪ At a given PaO_2 → more O_2 is bound to Hb (+++ affinity of Hb to O_2). <u>2- Effect of CO (carbon monoxide):</u> ▪ Affinity of CO for O_2-binding sites on Hb is 200 times more than O_2. ▪ CO binds to Hb → carboxy-Hb (COHb) ▪ Remaining Hb binding sites are strongly bound to O_2 → shift the curve to left. <u>3- Fetal hemoglobin:</u> ▪ Fetal Hb: pair of α & pair of γ polypeptide chains ▪ γ chains can't bind to 2,3-DPG → +++ affinity of Hb to O_2 → shift to left

O_2 dissociation curve of myoglobin:

- Myoglobin has 1 Fe^{++} atom, which can combine with 1 O_2 molecule.
- O_2 dissociation curve of myoglobin → rectangular hyperbola → horizontal till very low O_2 tension then suddenly descends vertically.
- Myoglobin → store O_2 till very low O_2 tension (severe exercise) → it gives its O_2

Carbon Dioxide Transport by Blood

100 ml of arterial blood contain 48 mL CO_2:

<u>1- CO_2 dissolved physically in plasma:</u> <u>(3ml/100ml = 5%)</u> → PCO_2 = 40mmHg

<u>2- CO_2 in chemical combination:</u>

a- **<u>As bicarbonate:</u>** <u>(42ml/100ml= 89%)</u> → $KHCO_3$ in RBCs & $NaHCO_3$ in plasma

- Plasma $NaHCO_3$ → **<u>alkaline reserve</u>**, → important in acid-base balance.

b- **<u>As carbamino compounds</u>**: (3 ml/100ml= 6%) (with Hb & plasma protein)

<u>Tidal CO_2</u>: Amount of CO_2 given by tissues to 100ml venous blood = 4ml at rest

- Mainly carried in chemical combination → blood pH does not markedly change.

Transport of tidal CO_2:

1- **In physical solution (0.4 ml)** → PCO_2 in venous blood 46 mmHg

2- **As carbamino compounds (1ml).**

3- **As bicarbonate (2.6 ml).**

i- At the tissues:

- CO_2 tension in tissues > CO_2 tension in arterial blood
- CO_2 diffuses into RBCs (carbonic anhydrase → faster reaction (1000 times))

CO_2 + H_2O Carbonic anhydrase → H_2CO_3 ⇌ H^+ + HCO_3^-

- ++++ HCO_3^- in RBCs → HCO_3^- diffuse out into plasma
- K^+ can't move in association with HCO_3^- (RBCs membrane is less permeable to cations). So Cl^- moves from plasma to RBCs to maintain electric neutrality
- This is known as chloride shift or Hamburger phenomenon.
- It is facilitated by Cl / HCO_3 exchanger in RBCs membrane.
- H^+ is buffered by deoxyhemoglobin (HHb) (weaker acid than oxyhemoglobin)
- Extra H^+ are buffered by plasma proteins in plasma.
- **Due to this shift of ions the following results occur:**

- +++ Bicarbonate content in both RBCs & plasma
- ---- pH of both RBCs & plasma (7.40 -7.37)
- +++ Cl^- in RBCs & --- Cl^- in plasma
- Constant Na^+, K^+ in RBCs & plasma (impermeable membrane to cations)
- +++ osmotic pressure of RBCs (+++ HCO_3^- & Cl^- → H_2O moves by osmosis).
- +++ RBCs volume & haematocrite value in venous blood

ii -At the lungs:

- On exposure to a low tension of CO_2, the opposite effect occurs.
- HCO_3^- shifts from plasma to R.B.Cs to be converted to CO_2 for exhalation.
- Cl^- returns from RBCs to plasma.

Control of Respiration

Respiratory Center (RC):

Pacemaker neurons in **Pre-Bottzinger area** in medulla →1ry generators for automatic respiration

I- Medullary Respiratory Centers:

	Dorsal Respiratory Group DRG	Ventral Respiratory VRG
Site	▪ dorsomedial in medulla ▪ bilateral in NTS (of vagus, glossopharyngeal)	▪ ventrolateral
Nature	▪ inspiratory neurons ▪ inherent (intrinsic) rhythm = 1ry inspiratory center ▪ Inspiratory Ramp Signals: weak signals & +++ gradually (ramp) for 2 sec, then stop for 3 sec => passive expiration. Ramp signal => gradual smooth inspiration • Project to pre-Botzinger pacemaker neurons	▪ inspiratory & expiratory neurons ▪ Have no rhythm (remain inactive during normal quiet breathing).
Receive from	a.Excitatory impulses from APC b. Inhibitory impulses from lung stretch receptors & PNC	excitatory impulses from DRG in hyperventilation
Send efferent to	a. Inspiratory muscles: diaphragm & external intercostal muscles. b. VRG (during forced breathing).	a. forced expiratory muscles b. forced inspiratory muscles
Function	normal quiet breathing	hyperventilation

II- Pontine Respiratory Centers:

	Apneustic Center APC	Pneumotaxic Center PNC
Site	▪ Lies in lower pons.	▪ Lies in the upper pons.
Receive from	▪ **inhibitory impulses from:** a- vagus (Hering Breuer reflex). b- PNC	**excitatory impulses from** Apneustic center
Send to	▪ stimulatory impulses to PNC & DRG	inhibitory impulses to APC &DRG
Function	▪ "Switch on" inspiration by sending regular continuous signals to DRG	"Switch off" inspiration: ---- APC → expiration → adjusts normal RR

Genesis Of Rhythmic Respiration:

- Respiratory rhythm is initiated from pacemaker cells in pre-Bottzinger area.
- Medullary centers alone can maintain automatic respiration (irregular)
- Their activity is modified by pontine centers
- APC → continuous regular discharge → excite the inspiratory neurons of DRG
- DRG sends impulses → spinal cord → diaphragm & external intercostals.

- Contraction of these muscles → expansion of chest & inflation of lungs.
- APC is inhibited by regular impulses from (1) Pneumotaxic center and (2) lung stretch receptors via vagus nerve.
- Inspiration is switched off → starts expiration => cycle repeats itself.

Experimental Evidence:

Cutting the two vagi

- Respiration becomes slower and deeper

Transection at mid pons separating PNC from APC:

Slightly slow & deep respiration

Transection at mid pons + cutting both vagi:

- APC now receives no inhibition → continuously stimulate inspiration
- Breathing stops in full inspiration (apneusis) or inspiratory spasms interrupted by intermittent expiration (apneustic breathing).

(A)- Chemical regulation of respiration

1- Central chemoreceptors:

1- Site:

- bilaterally just beneath the ventral surface of medulla near RC neurons.
- Protected by blood brain barrier. Small, soluble, uncharged O_2, CO_2 diffuse through

2- Stimulus: Central chemoreceptors are H^+ receptors

a. Response of central chemoreceptor to CO_2:

- CO_2 has a very potent indirect effect by changing CSF-H^+ concentration.
- CO_2 crosses the BBB where it: $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow HCO_3^- + H^+$
- H^+ will stimulate the central chemoreceptors.
- **CSF Buffering:**
  - CSF has only small amount of protein (20 mg/100ml) compared to plasma (7000 mg/100 ml), → not highly buffered as blood.
  - A small change in arterial PCO_2 results in large changes in CSF pH

    3% +++ in $PaCO_2$ => double ventilation

b. Response of central chemoreceptor to H^+ (1^{ry} stimulus):

- H^+ in CSF → the only direct stimulus for central chemoreceptors which respond to changes in pH of brain ECF & cerebrospinal fluid (CSF)
- H^+ ions in blood → don't cross BBB; thus changes in blood H^+ (metabolic acidosis & alkalosis) → no effect on central chemoreceptors.

2- Peripheral chemoreceptors:

1- Site: glomus cells in small nodules on aorta (few) & carotid artery (most):

- Aortic bodies: aortic arch
- Carotid bodies: at bifurcation of common carotid artery

2- Innervations: (buffer nerves)

- carotid bodies => Hering's nerve (branch of glossopharyngeal)
- aortic bodies => vagus nerve.

3- Stimulus:

a- Response of peripheral chemoreceptors to decreased arterial PO_2:

- Hypoxia is the most potent stimulus for peripheral chemoreceptors.
- Very high blood flow, 20ml/min/gm
- So, O_2 needs of the cells are supplied by dissolved O_2 alone.
- Monitor PO_2 = dissolved O_2 rather than O_2 content (Hb-O_2) of arterial blood.
- Not sensitive to changes in O_2 content caused by anemia, met-Hb or CO
- ---- blood flow markedly (hemorrhage) → +++ peripheral chemoreceptors

b- Response of peripheral chemoreceptors to changes in arterial H^+:

Metabolic acidosis → +++ H^+ → +++ peripheral chemoreceptors → +++ RR

Metabolic alkalosis → ---- H^+ → --- peripheral chemoreceptors → ---RR

c- Response of peripheral chemoreceptors to +++ arterial PCO_2:

- 30% of ventilatory response to CO_2 => through peripheral chemoreceptors either directly or indirectly by inducing an increase in arterial H^+ concentration.

Ventilatory response to O_2 lack:

Hypoxia is a weak stimulus for respiration than CO_2 excess because:

- Hypoxia stimulates the respiration only through peripheral chemoreceptors. While, CO_2 has stimulatory effect on central & peripheral chemoreceptors.
- O_2 lack → +++ RR → CO_2 wash => ---- PCO_2 => --- RR (counterbalance the stimulatory effect of O_2 lack)
- **When PO_2 decreases from 100 - 60 mmHg (plateau part of curve):** Ventilation is doubled.
- **When PO_2 decreases from 60 - 30 mmHg (steep part of curve):** marked increase in ventilation is observed (it increases 6 times)
- **At PO_2 20 mmHg:** Drop of arterial PO_2 to 20 mmHg or less has a direct inhibitory effect on the respiratory center (brain hypoxia)

Hypoxia is the major controller of breathing in case of:

- Depression of RC by narcotics or anaesthetics (inhibited central chemoreceptors). Don't treat this patient by pure $O_2 \rightarrow$ the driving effect of O_2 lack on respiration will be abolished.

Ventilatory responses to changes in CO_2:

CO_2 excess is more effective stimulus for respiration than O_2 lack as it stimulates both central (more important) & peripheral chemoreceptors

PCO_2 is the major controller of respiration under normal conditions:

- 70% of the effect of PCO_2 is due to indirect +++ central chemoreceptors (+++CSF-H^+)
- 30% of the effect of PCO_2 is due to +++ peripheral chemoreceptors either directly or by inducing an +++ H^+ in arterial blood.
- Small ++ PCO_2 (3%) $\rightarrow$ marked +++ in ventilation (doubled)
- +++ CO_2 to 6% in inspired air => +++ ventilation 6 times.
- +++ CO_2 to 10% in inspired air => +++ ventilation 10 times.
- +++ CO_2 to 20% or more => respiratory depression, then death.
- Arterial PCO_2 is stabilized near the normal value (40 mmHg).
- CO_2 narcosis: +++$PaCO_2$ (hypercapnea) > 70 mmHg $\rightarrow$ depresses CNS even RC

Ventilatory response due to changes in acid-base balance:

- The normal pH of arterial blood is 7.4. (<7 or >7.8 $\rightarrow$ incompatible with life)
- $H^+ \propto PCO_2 / HCO_3^-$; Ratio between HCO_3^- and CO_2 must remain constant

1- Changes in blood pH affect pulmonary ventilation:

a- Metabolic acidosis

- Addition of fixed acids to blood (lactic acid in exercise, keto-acids in diabetes)
- +++ $H^+ \rightarrow$ +++peripheral chemoreceptors $\rightarrow$ +++RR $\rightarrow$ --- $CO_2 \rightarrow$ pH returns to normal (compensated acidosis)

b- Metabolic alkalosis

- +++HCO_3^- in blood (ingestion of HCO_3^- for treatment of peptic ulcer or vomiting)
- --- $H^+ \rightarrow$ --- peripheral chemoreceptors $\rightarrow$ ---RR $\rightarrow$ +++ $CO_2 \rightarrow$ pH returns to normal (compensated alkalosis)

2- Changes in pulmonary ventilation affect the blood pH:

a- Respiratory acidosis

+++ H^+ due to 1^{ry} pulmonary hypoventilation $\rightarrow$ +++ P_aCO_2 & acidosis

- **Afferents:** reach the medulla via trigeminal nerve.
- **Response:** Deep inspiration followed by forced expiration against open glottis
- **Results:** sever rush of air to outside getting rid of irritants

B- Coughing Reflex:

- **Receptors:** irritant receptors in mucosa of trachea, larynx and bronchi.
- **Stimulus:** mechanical (dust, mucus, food) or chemical (smoke, fumes)
- **Afferents**: reach the medulla via vagus nerve.
- **Response:** Deep inspiration followed by forced expiration while the glottis is closed => marked rise in intra-abdominal pressure (up to 100 mmHg)
- **Results:** glottis suddenly opens → air is expelled out => push away irritants

C- Lung stretch receptors:

- **Receptors:** stretch receptors within smooth muscles of bronchi & bronchioles
- **Stimulus:** lung inflation and airway distention.
- **Afferents:** vagus nerve.
- **Response:** Hering Breuer (Lung Inflation) Reflex.

D- Lung irritant receptors:

- **Receptors:** irritant receptors in the mucosa of bronchi and bronchioles.
- **Stimulus:** mechanical or chemical irritants
- **Afferents:** vagus nerve.
- **Response:**
  - Coughing is an attempt to expel the irritant substance.
  - Bronchospasm limit penetration of dangerous substances to the lungs.

F- J- Receptors (Juxta-capillary):

- **Receptors:** present in alveolar walls close to pulmonary capillaries
- **Stimulus:** +++ pulmonary capillary pressure (pulmonary congestion)
- **Afferents:** Vagus nerve.
- **Response:**
  - Tachypnea and dyspnea.
  - no role in normal breathing; sensation of dyspnea in lung & heart diseases

III- Respiratory reflexes arising from cardiovascular system:

1- Afferents from arterial baroreceptors (High pressure receptors)

- **Receptors:** in aortic arch and carotid sinus.
- **Stimulus**: changes ABP and pulse pressure.

b- **Respiratory alkalosis**

- --- H^+ is due to 1ry pulmonary hyperventilation → --- P_aCO_2 & alkalosis
- Respiratory acidosis and alkalosis are corrected by the kidneys.

Non Chemical Regulation of Respiratory Activity

I- Afferents from higher centers:

1- Cerebral cortex: Responsible for **voluntary respiration:**

Cerebral cortex can override the function of RC in brain stem (within limits)

Example: Talking, singing & playing wind instruments

Pathway: Cerebral cortex → regulates RC neurons or directly send corticospinal & corticobulbar tracts to AHCs of respiratory muscles

Experimentally:

a- **Voluntary hyperventilation** done with limited duration (PCO_2 will decrease)

b- **Voluntary apnea (Breath holding)**

We can voluntarily stop breathing (swimming) for 45-60 sec, after that we have uncontrollable desire to breathe → break point due to --- PO_2 & +++ PCO_2.

At this point, chemical drive to respiration overwhelms voluntary suppression

Duration of voluntary apnea can be prolonged 15-20 sec **by:**

- Initial hyperventilation before breath holding
- Prior inhalation of pure O_2
- Hold the breath in full inspiration → +++ pulmonary stretch receptors → --- RC
- Swallowing.

2- Limbic system: Pain & emotions → affect respiration

3- Hypothalamus contains:

- Higher parasympathetic centers: when stimulated → --- respiration (pain).
- Higher sympathetic centers: when stimulated → +++ respiration (emotions).
- Temperature regulating centers: when stimulated → +++ respiration (fevers)

II- Afferents from respiratory tract:

1- Afferents from Upper respiratory passages

A- Sneezing Reflex:

- Receptors: irritant receptors of nasal mucosa.
- Stimulus: mechanical or chemical irritants.

- **Afferents:** branches of vagus & glossopharyngeal n.
- **Response:** +++ ABP → +++ baroreceptors → ---- RC → --- RR → --- VR → --- CO → ---ABP back to normal
- ---- ABP (hemorrhage) → ---- inhibitory impulses from arterial baroreceptors to RC → +++ respiration → +++ VR → +++ CO → +++ ABP
- NE or large doses of adrenaline → +++ ABP → ---- RC → adrenaline apnea

2- **Afferent & from atrial receptors (Low pressure receptors)**

- **Receptors:** in right atrium, big veins
- **Stimulus:** changes in venous return and central venous pressure.
- **Afferents**: vagus
- **Response:** +++ VR → +++ these receptors → vagus → +++ RC (+++ RR during exercise = Harrison's reflex) → lungs can oxygenate the extra amounts of VR

Hypoxia

Definition: O_2 deficiency at tissue due to ---O_2 supply or ---O_2 utilization ability

I- Hypoxic Hypoxia

Definition: inadequate oxygenation of arterial blood (--- PaO_2) → arterial hypoxia.

Characteristics: ---PO_2 & O_2 content in arterial & venous blood

Signs: generalized cyanosis.

Causes:

1. Low O_2 tension in inspired air as in high altitudes or in mines.
2. **Pulmonary disorders:**

a- **Impaired ventilation:**

- Depression of medullary RC by morphine; barbiturates; anaesthetics
- Obstructive diseases → bronchial asthma, tumors, emphysema
- Restrictive diseases in lungs (collapse, fibrosis) or chest cage (kyphoscoliosis...)

b- **Impaired Diffusion:**

- --- surface area for diffusion (lobectomy or pneumonectomy).
- +++thickness of pulmonary membrane (Pneumonia, edema, fibrosis)

c- **Ventilation Perfusion imbalance:** low V_A/Q → impairment of O_2 transfer

3. **Shunting of venous blood into arterial blood:**

Congenital intra-atrial septal defects

II- Anemic Hypoxia

Definition: deficiency of Hb capable of carrying O_2.

Characteristics: ---- Hb → ---O_2 content of arterial blood but normal PO_2. Extraction of normal amount of O_2 at tissues → --- O_2 content & PO_2 in venous blood

Causes:

1. Insufficient Hb in all anemias:

- At rest, hypoxia is not severe; because +++ 2,3 DPG in RBC => Hb-O_2 curve shift to right => --- Hb affinity to O_2
- At exercise, hypo6hyxia is severe because +++ O_2 needs of tissues.

2. Abnormal forms of Hb:

a- **CO poisoning:**

Cause: CO exposure, formed by incomplete combustion of carbon or gasoline

CO is toxic because:

- Binds at same site of O_2 on Hb → carboxy-Hb → can't carry O_2.
- Hb has 210 times more affinity for CO than O_2.
- CO-Hb amount depends on duration of exposure & CO amount in air.
- Death occurs when 70-80% of Hb is converted to CO-Hb.
- CO-Hb breaks down slowly.
- CO-Hb → +++ affinity of rest of Hb to O_2 (shift to left)→ weak release of O_2

Signs: CO-Hb has cherry red color → appear in skin, mucus membrane

1. Headache, nausea, loss of judgment
2. peripheral chemoreceptors are not stimulated (normal PO_2) → normal RR

Treatment:

- Termination of exposure.
- Hyperbaric O_2 under high pressure (1-3 atmosphere)
- 95% O_2 + 5% CO_2: better as CO_2 stimulates respiration & --- affinity of Hb to CO)
- Blood transfusion.

b. **Met Hemoglobin**

Cause: oxidation of heme Fe^{++} to Fe^{+++} by oxidizing agents (nitrates, chlorates)

Signs: bluish color, appears in skin and mucus membranes.

c. **Sulf Hemoglobin**

Cause: due to reducing agent (rare)

Signs: dull bluish color

III- Stagnant Hypoxia

Definition: inadequate blood flow through tissues/ slow circulation → prolong time of contact between blood & tissues → insufficient O_2 supply to tissues

Characters: Slow blood flow in capillaries → tissues withdraw extra amount of O_2 → normal PO_2 & content in arterial blood but ----PO_2 & O_2 content in venous blood

Signs: Generalized or localized cyanosis

Causes:

1. **Generalized:** ----blood flow to whole body (congestive heart failure or shock)
2. **Localized:** ----blood flow to localized area of body (thrombosis or embolism)

IV- Histotoxic Hypoxia

Definition: tissues can't utilize O_2 due to inhibition of cytochrome enzymes by toxins

Characteristics: normal O_2 delivery to tissues but tissues don't consume it => normal PO_2 & content in arterial blood, but +++ PO_2 & content in venous blood.

Signs: No cyanosis

Causes:

1. Cyanide poisoning: inhibits cytochrome oxidase, so cytochrome remains reduced.
2. Alcohol, narcotic poisoning: block dehydrogenase → cytochrome remains oxidized

Oxygen Therapy in different types of Hypoxia

O_2 therapy is Highly beneficial	O_2 therapy is less beneficial	O_2 therapy is not beneficial
1. Hypoxic hypoxia due to: a. decreased atmospheric PO_2. b. hypoventilation. c. impaired diffusion. 2. Carbon monoxide poisoning.	1. Hypoxic hypoxia due to A-V shunt 2. Anemic hypoxia 3. Stagnant hypoxia	▪ Histotoxic hypoxia where tissues cannot utilize PO_2.

Cyanosis

Definition: Bluish coloration of skin & mucous membranes due to presence of +++ amounts of reduced (deoxygenated) Hb in capillaries

Threshold of cyanosis: 5 gm reduced Hb /100 ml capillary blood.

Reduced Hb (blue) → visible where thin skin (lips, mucous membrane, nail beds)

Types of cyanosis: 1. Generalized (or central) cyanosis

2. Localized (or peripheral) cyanosis

Causes of cyanosis: 1. Hypoxic hypoxia

2. Stagnant hypoxia

Relation between hypoxia and cyanosis:

Cyanosis appear with	Cyanosis does not appear with
1. Hypoxic hypoxia: --- % saturation of Hb with O_2 in arterial & venous blood 2. Stagnant hypoxia: low blood flow → extra amounts of O_2 are removed from Hb	1. Anemic hypoxia: → --- Hb amount (both oxygenated & deoxygenated) 2. Histotoxic hypoxia: → no reduced Hb. 3. CO poisoning: cherry red color of CO-Hb

- **Cyanosis can be mistaken** with bluish color of met-Hb and sulph-Hb

Intensity of cyanosis is not a reliable sign for degree of hypoxia:

They do not run parallel in hypoxic hypoxia:

1. If bleeding occurs: Decrease in oxy-Hb → more hypoxia
   Decrease in reduced Hb → less cyanosis
2. With acclimatization: (polycythemia)
   Increase in oxy-Hb → less hypoxia
   Increase in reduced Hb → more cyanosis

Factors that modify the color of cyanosis:

1. **Total amount of Hb:**
   - In anemia: cyanosis rarely appears
   - In polycythemia: cyanosis appears easily
2. **Amount of reduced Hb:**
   - Normally reduced Hb is about 2.6 gm/100 ml
   - Cyanosis appears in hypoxic & stagnant hypoxia (reduced Hb> 5g/100ml)
   - Cyanosis doesn't appear in anemic & histotoxic hypoxia
3. **Abnormal composition of blood:**
   - Met-Hb or sulph-Hb gives a bluish color, may be mistaken as cyanosis
4. **Skin:**
   - Thickness: Cyanosis appears in areas with thin skin (lips, ear lobes, nail beds)
   - Pigmentation: Cyanosis is masked in dark races.
5. **Cutaneous Blood flow**:
   - Exposure to heat → cutaneous VD → red skin
   - Exposure to cold → cutaneous VC → blue skin (cyanosis)
   - Exposure to severe cold → reactive VD